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Antibiotics and oral contraceptive failure — a case-crossover study☆

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Abstract

Background: Evidence on the association between antibiotic use and combined oral contraceptive (COC) failure is controversial. We examined the effect of concomitant antibiotic treatment on the risk of breakthrough pregnancy among COC users.
Study Designs: We performed a case-crossover study of 1330 COC failure cases among 17,721 women from the Slone Epidemiology Center Birth Defects Study (1997–2008) and among 25,941 women from the National Birth Defects Prevention Study (NBDPS, 1997–2005). Self-matched odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by comparing antibiotic use between the 4 weeks before conception ("case period") and the 4–8 weeks before conception ("control period") using conditional logistic regression. A case–time-control analysis was conducted using nonusers of COCs with unplanned pregnancies as controls.
Results: For the combined data, the self-matched OR was 1.08 (95% CI: 0.63–1.84) and the case–time-control OR was 1.12 (0.63–1.98) for antibiotics overall. The results did not appreciably differ when adjusted for characteristics that might vary between the case and control period. However, among COC failure cases from the NBDPS, allowing a 1-month gap between the case and control period resulted in a self-matched OR of 1.45 (0.85–2.50) and a case–time-control OR of 1.55 (0.86–2.79) for antibiotics overall.
Conclusions: We did not find an association between concomitant antibiotic use and the risk of breakthrough pregnancy among COC users. However, due to limited power and potential carryover effects, findings from this study cannot rule out an elevated risk of COC failure among antibiotic users.

Keywords: Antibiotics; Case-crossover study; Drug interactions; Epidemiology; Oral contraceptives; Pregnancy

1. Introduction

Studies have shown that the antibiotic rifampin is associated with a higher risk of unintended pregnancy among combined oral contraceptive (COC) users by inducing hepatic microsomal enzymes that decrease steroid hormone plasma levels [1–4]. However, whether other antibiotics interfere with the effectiveness of COCs is controversial. Some have suggested that broad-spectrum antibiotics (e.g., ampicillin) might decrease hormone plasma levels by interfering with the enterohepatic recirculation of hormone metabolites through a disruption of the intestinal bacterial flora [1–3]. Although package inserts of both broad-spectrum antibiotics and COCs warn of potential COC

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failure with concomitant antibiotic use, it has been argued that antibiotics other than rifampin do not seem to significantly affect plasma levels of COC steroids, and women taking COCs and antibiotics concomitantly do not appear to have a greater risk of breakthrough pregnancy. Given the serious consequences of unwanted pregnancies, it is critical to resolve this important source of confusion.

We conducted a study to assess the effect of concomitant antibiotic use on COC failure. The study also illustrated the application of case-only self-matched study design in the studies of drug–drug interactions [5] when the use of one of the drugs is transient.

2. Methods

2.1. Data source

We used data from the Slone Epidemiology Center Birth Defects Study (BDS) and the National Birth Defects Prevention Study (NBDPS). These two multicenter case-control surveillance programs of birth defects represent the largest interview-based data sources on prenatal exposure and birth defect outcomes in the United States. The BDS has been approved by the relevant institutional review boards at Boston University and participating hospitals; the NBDPS has been approved by the institutional review boards of CDC and the participating study centers.

Since 1976, the BDS has interviewed more than 37,000 mothers of babies with and without birth defects from the greater metropolitan areas of Philadelphia, San Diego and Toronto, as well as from selected regions in Iowa, Massachusetts and New York State [6,7]. Study subjects are identified through review of admissions and discharges at major birth hospitals and pediatric referral hospitals and clinics, logbooks in newborn intensive care units, through weekly telephone contact with collaborators at newborn nurseries in community hospitals and through collaborations with state birth defects registries. Mothers provide informed consent before participation.

The NBDPS, established in 1997, is an on ongoing population-based, case-control study. The 10 participating sites (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas and Utah) identify cases with any of approximately 30 birth defects from birth defect surveillance systems and a random sample of non-malformed controls from birth certificates or hospital records. The NBDPS has been described in detail elsewhere [8].

In the BDS, mothers who agree to participate were interviewed within 6 months of delivery, while in the NBDPS, the interview window was between 6 weeks and 24 months of delivery. The sampling scheme of the BDS and the NBDPS ensures that no woman is included in both studies.

In both BDS and NBDPS, mothers were interviewed by trained interviewers using a computer-assisted telephone interview. The interview, which takes about 1 h to complete and can be conducted in either English or Spanish, collects information on demographics, lifestyle factors, dietary intake, occupational exposure, reproductive factors, pregnancy planning and medical factors. Although some women did not respond to it, a question about whether the pregnancy was intended is asked in both studies. Specifically, the BDS asks, “At the time that you became pregnant, did you (a) want to become pregnant then, (b) did you want to wait until later, or (c) did you not want to become pregnant at all?”; the NBDPS asks, “At the time you became pregnant with (index baby), did you want to become pregnant then, did you want to wait until later, or did you not want to become pregnant at all?”

The interview also includes detailed questions about use of medications (prescription, over-the-counter, vitamins/minerals and herbal products) that occurred from 2 months before the last menstrual period (in the BDS) or from 3 months before conception (in the NBDPS) through the end of the pregnancy. Medications are coded by means of the Slone Drug Dictionary (http://slone-web.bu.edu/slonedrug-dictionary). When possible, reported medications are verified by asking the woman to read information from the medication container. Identification of timing of drug exposure is facilitated by use of a calendar covering periods before and after pregnancy; special dates (e.g., last menstrual period, holidays) are marked to help enhance recall. Data are also collected on duration, frequency, indication, form and number of pills per day.

2.2. Study population

We identified 17,721 women interviewed in BDS from 1997 to 2008 and 25,941 in NBDPS from 1997 to 2005. A total of 1330 (387 from the BDS, 943 from the NBDPS) reported the pregnancies were unplanned and were using COCs to prevent pregnancy during the month before and at least part of the month after their estimated date of conception (i.e., 14 days after the last menstrual period). These women were considered cases of COC failure under the assumption that they were taking COCs continuously but still had a breakthrough pregnancy. The results (not shown) were materially unchanged when we modified the definition of COC failure cases by requiring women to use COCs from the month before to at least part of the second month after their estimated date of conception. Users of progestin-only OCs were excluded from the study.

2.3. Statistical analysis

Because both studies were restricted to women who had been pregnant, we did not have data on women who used COCs, with or without concomitant antibiotic therapy, who did not become pregnant. Therefore, we could not estimate the rate ratio of pregnancy (i.e., rate ratio of COC failure) associated with antibiotic use among COC users by comparing pregnancy rates among women exposed and not exposed to antibiotics. Instead, we used a case-crossover design, where cases served as their own controls (Fig. 1),

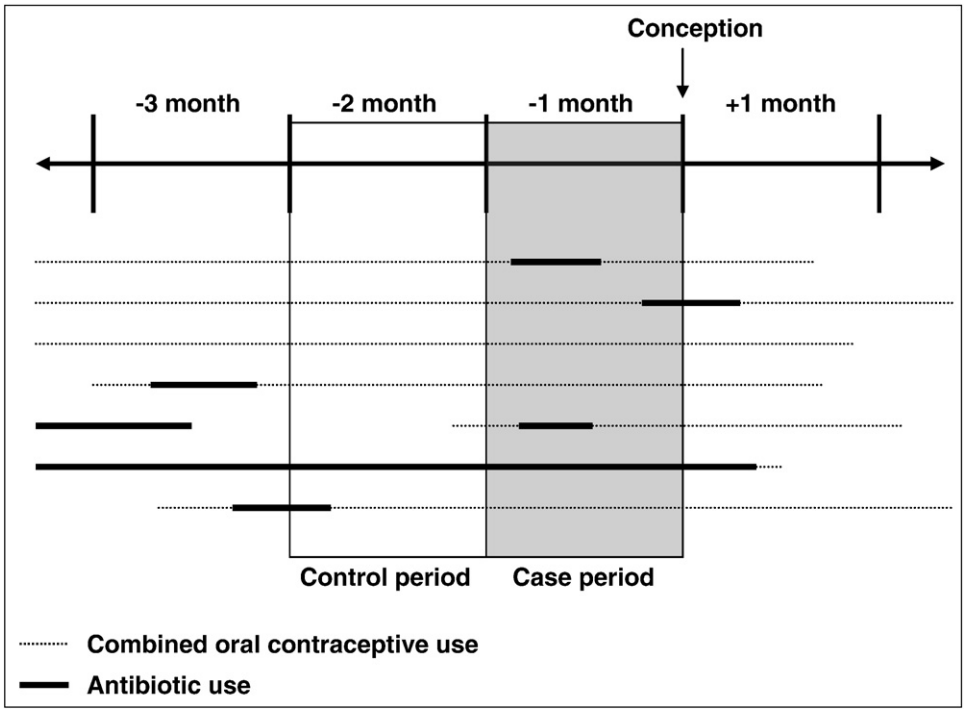

Fig. 1. A case-crossover design for concomitant antibiotic use and COC failure. COC failure cases were women who used COCs during the month before and the month after the estimated date of conception. Each line represents a woman; the lines illustrate a sample of possible COC and antibiotic use patterns around conception.

to examine whether antibiotic use before the time of breakthrough pregnancy was significantly different from the usual frequency among women with COC use [9,10]. In doing so, we evaluated the prevalence of antibiotic use during the 4 weeks preceding the date of conception ("case period"), which is presumably the period when antibiotics might be most likely to affect the risk of breakthrough pregnancy, and compared it with the 4–8 weeks before the date of conception ("control period"), which provided an estimate of the expected prevalence of antibiotic use for each case. Using conditional logistic regression, we estimated a self-matched odds ratio (OR) by the ratio of the discordant pairs, i.e., the ratio of the number of women exposed only during the case period to the number of women exposed only during the control period.

The case-crossover approach effectively eliminates potential confounding effects from both measured and unmeasured subject characteristics that are constant during the case and control period (e.g., sociodemographic and genetic factors), but does not adjust by design for time-varying factors [9,10]. We used multivariable conditional logistic regression models to adjust for confounding by transient factors potentially associated with both the use of antibiotics and conception (e.g., infections). We assumed no-carryover effect and that the underlying subject-specific probability of being exposed to antibiotics among COC users was constant within the interval between the control and the case period.

To account for the potential time trends in antibiotic use between the case and control period, we performed a case–time-control analysis [10,11] using as a control group 16,896 (5941 from the BDS, 10,955 from the NBDPS) non-COC users with unplanned pregnancies. We estimated the expected time trends of antibiotic use around conception among COC failure cases using the information from the control women through a self-matched OR for antibiotic use. We removed the potential effect of time from the case-crossover effect estimate by dividing the OR obtained among COC failure cases by the OR obtained in the control group, assuming that the control women provide an unbiased estimate of such trend for the cases [10–12].

To examine the assumption of no-carryover effect, we used data from NBDPS where history of medication use is collected up to 3 months before conception (in contrast to the 2-month window prior to the last menstrual period used by the BDS); the control period was defined as the third month prior to the conception in this analysis, therefore leaving a "wash-out" gap of 1 month between the case and control period.

Whenever possible, we repeated our analysis by antibiotic class (e.g., macrolides), indications for antibiotic therapy (e.g., urinary tract infection), cigarette smoking (never/ever), alcohol drinking (never/ever) and pre-pregnancy body mass index (<25 and ≥ 25 kg/m^2). We did not stratify by dosage of estrogen component in COCs because the large majority of women in both studies had a low-dose regimen. Also, because most antibiotics used by study women were

considered broad-spectrum, we did not estimate the effects of broad- and narrow-spectrum antibiotics separately. Finally, since recall of medication use may differ across periconceptional months (e.g., women may be particularly aware of their medication use around conception), we also estimated the effect of acetaminophen and ibuprofen, often used concomitantly with antibiotics but not thought to be associated with the risk of COC failure.

3. Results

The baseline characteristics for COC failure cases and non-OC users with unplanned pregnancies are shown in Table 1. Compared to non-OC users with unplanned pregnancies, women with breakthrough pregnancies while taking COCs were in general younger, more likely to be non-Hispanic white, had a lower education level, more likely to be obese and more likely to smoke or drink alcohol. These differences were observed in both BDS and NBDPS, and in the combined population.

Among women with COC failure, the prevalence of antibiotic use was 3.6% during the 4 weeks before the date of conception (case period) and 3.9% during the 4–8 weeks preceding the date of conception (control period) in the BDS; the corresponding prevalence was 4.1% and 3.8% in the NBDPS (Fig. 2). When the two data sources were combined, the prevalence of antibiotic use was 4.0% during the case period and 3.8% during the control period. More than 80% of the antibiotics had a treatment duration of 14 days or less. Amoxicillin and ampicillin were the most commonly used antibiotics, followed by macrolides and sulfonamides.

Although there were some variations between the prevalence of periconceptual antibiotic use in the BDS and NBDPS, there was no evidence that the results differed by the two data sources (p value of test for heterogeneity of ORs was >.05); we therefore combined data from the BDS and NBDPS to provide more robust estimates (Table 2). Among women with COC failure, 28 had used antibiotics only during the case period and 26 only during the control period, giving a self-matched OR of 1.08 (95% CI: 0.63–1.84). For specific antibiotics, only ampicillin/amoxicillin had at least five discordant pairs in each of the case (18 discordant pairs) and control period (15 discordant pairs), with an OR of 1.20 (0.60–2.38). Due to small sample sizes, the effects of other specific antibiotics were not further explored.

When we adjusted for occurrence of urinary tract infection and upper respiratory tract infection, which might change between the case and control period, the OR was 1.10 (0.63–1.93) for antibiotics overall. We did not find strong

Table 1
Baseline characteristics for COC failure cases and non-OC users with unplanned pregnancies

Characteristics	The Slone Epidemiology Center Birth Defects Study		The National Birth Defects Prevention Study		Combined	
	COC failure cases (*n*=387)	Non-OC users with unplanned pregnancies (*n*=5941)	COC failure cases (*n*=943)	Non-OC users with unplanned pregnancies (*n*=10,955)	COC failure cases (*n*=1330)	Non-OC users with unplanned pregnancies (*n*=16,896)
Maternal age (years)						
<20	49 (12.7)	797 (13.4)	176 (18.7)	2291 (20.9)	225 (16.9)	3088 (18.3)
20–24	125 (32.3)	1293 (21.8)	315 (33.4)	2929 (26.7)	440 (33.1)	4222 (25.0)
25–29	115 (29.7)	1323 (22.3)	238 (25.2)	2588 (23.6)	353 (26.5)	3911 (23.2)
30–34	61 (15.8)	1355 (22.8)	154 (16.3)	1993 (18.2)	215 (16.2)	3348 (19.8)
≥35	37 (9.6)	1153 (19.4)	60 (6.4)	1153 (10.5)	97 (1.3)	2306 (13.7)
Unknown	0 (0.0)	20 (0.3)	0 (0.0)	1 (0.0)	0 (0.0)	21 (0.1)
Maternal race/ethnicity						
Non-Hispanic white	267 (69.0)	3363 (56.6)	560 (59.4)	5709 (52.1)	827 (62.2)	9072 (53.7)
Hispanic	57 (14.7)	1161 (19.5)	216 (22.9)	2707 (24.7)	273 (20.5)	3868 (22.9)
Non-Hispanic black	45 (11.6)	907 (15.3)	120 (12.7)	1608 (14.7)	165 (12.4)	2515 (14.9)
Other	18 (4.7)	506 (8.5)	45 (4.8)	887 (8.1)	63 (4.7)	1393 (8.2)
Unknown	0 (0.0)	4 (0.1)	2 (0.2)	44 (0.4)	2 (0.2)	48 (0.3)
Maternal education (years)						
≤12	155 (40.1)	2761 (46.5)	435 (46.1)	5630 (51.4)	590 (44.4)	8391 (49.7)
13–15	136 (35.1)	1532 (25.8)	339 (36.0)	2858 (26.1)	475 (35.7)	4390 (26.0)
>15	96 (24.8)	1641 (27.6)	154 (16.3)	2192 (20.0)	250 (18.8)	3833 (22.7)
Unknown	0 (0.0)	7 (0.1)	15 (1.6)	275 (2.5)	15 (1.1)	282 (1.7)
Pre-pregnancy body mass index						
<18.5	19 (4.9)	323 (5.4)	70 (7.4)	692 (6.3)	89 (6.7)	1015 (6.0)
18.5–24.9	214 (55.3)	3238 (54.5)	462 (49.0)	5404 (49.3)	676 (50.8)	8642 (51.2)
25.0–29.9	83 (21.5)	1289 (21.7)	195 (20.7)	2370 (21.6)	278 (20.9)	3659 (21.7)
≥30.0	65 (16.8)	928 (15.6)	188 (19.9)	1952 (17.8)	253 (19.0)	2880 (17.1)
Unknown	6 (1.6)	163 (2.7)	28 (3.0)	537 (4.9)	34 (2.6)	700 (4.1)
Cigarette smoking	217 (56.1)	2788 (47.0)	375 (39.8)	4239 (38.7)	592 (44.5)	7027 (41.6)
Alcohol intake	189 (48.8)	2462 (41.1)	476 (50.5)	5176 (47.3)	665 (50.0)	7638 (45.2)

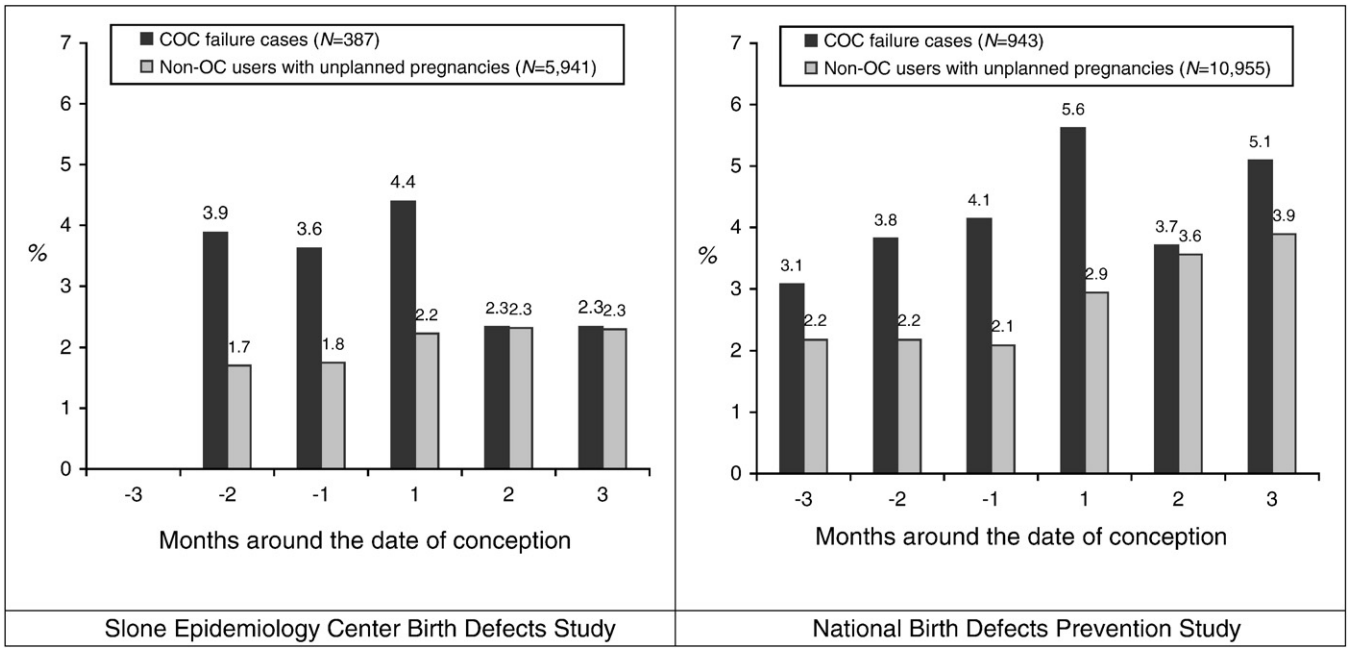

Fig. 2. Use of antibiotics around the months of conception among COC failure cases and non-OC users with unplanned pregnancies. COC failure cases were women who used COCs during the month before and the month after the estimated date of conception. The Slone Epidemiology Center Birth Defects Study (1997–2008) and the National Birth Defects Prevention Study (1997–2005).

Table 2
The association between antibiotic use and the risk of COC failure

No gap between case and control period[a]	The Slone Epidemiology Center Birth Defects Study		The National Birth Defects Prevention Study		Combined	
Case-crossover analysis	*Discordant pair ratio*	*Odds ratio (95% confidence interval)*	*Discordant pair ratio*	*Odds ratio (95% confidence interval)*	*Discordant pair ratio*	*Odds ratio (95% confidence interval)*
Antibiotic overall	8/9	0.89 (0.34–2.30)	20/17	1.18 (0.62–2.25)	28/26	1.08 (0.63–1.84)
Amoxicillin/ampicillin	6/4	1.50 (0.42–5.32)	12/11	1.09 (0.48–2.47)	18/15	1.20 (0.60–2.38)
Acetaminophen	8/14	0.57 (0.24–1.36)	27/30	0.90 (0.54–1.51)	35/44	0.80 (0.51–1.24)
Ibuprofen	3/5	0.60 (0.14–2.51)	9/18	0.50 (0.22–1.11)	12/23	0.52 (0.26–1.05)
Case–time-control analysis	*Time trend OR*	*Odds ratio (95% confidence interval)*	*Time trend OR*	*Odds ratio (95% confidence interval)*	*Time trend OR*	*Odds ratio (95% confidence interval)*
Antibiotic overall	1.07	0.84 (0.30–2.35)	0.93	1.26 (0.64–2.51)	0.96	1.12 (0.63–1.98)
Amoxicillin/ampicillin	1.23	1.22 (0.31–4.88)	0.97	1.13 (0.46–2.74)	1.04	1.16 (0.55–2.45)
Acetaminophen	0.81	0.71 (0.29–1.75)	1.56	0.61 (0.36–1.02)	1.27	0.65 (0.41–1.01)
Ibuprofen	0.58	1.04 (0.24–4.52)	0.77	0.66 (0.30–1.48)	0.71	0.75 (0.37–1.52)
A 1-month gap between case and control period[b]	The Slone Epidemiology Center Birth Defects Study		The National Birth Defects Prevention Study		Combined	
Case-crossover analysis	*Discordant pair ratio*	*Odds ratio (95% confidence interval)*	*Discordant pair ratio*	*Odds ratio (95% confidence interval)*	*Discordant pair ratio*	*Odds ratio (95% confidence interval)*
Antibiotic overall	–	–	32/22	1.45 (0.85–2.50)	–	–
Amoxicillin/ampicillin	–	–	17/11	1.55 (0.72–3.30)	–	–
Acetaminophen	–	–	32/25	1.28 (0.76–2.16)	–	–
Ibuprofen	–	–	13/20	0.65 (0.32–1.31)	–	–
Case–time-control analysis	*Time trend OR*	*Odds ratio (95% confidence interval)*	*Time trend OR*	*Odds ratio (95% confidence interval)*	*Time trend OR*	*Odds ratio (95% confidence interval)*
Antibiotic overall	–	–	0.94	1.55 (0.86–2.79)	–	–
Amoxicillin/ampicillin	–	–	0.92	1.69 (0.74–3.83)	–	–
Acetaminophen	–	–	1.55	0.84 (0.50–1.42)	–	–
Ibuprofen	–	–	0.73	0.90 (0.44–1.83)	–	–

[a] Case period: the 4 weeks preceding the date of conception; control period: the 4–8 weeks before the date of conception.
[b] Case period: the 4 weeks preceding the date of conception; control period: the 8–12 weeks before the date of conception.

evidence suggesting that specific indications for antibiotics were associated with COC failure, nor did we observe the effects of antibiotics varied by cigarette smoking, alcohol drinking and pre-pregnancy body mass index (results not shown), but our power to detect such effect modification was small.

In the case–time-control analysis, the OR for time trends of overall antibiotic use was 0.96 (0.79–1.18) in control women (non-OC users who did not plan to become pregnant). We divided the case-crossover OR by this OR and obtained a case–time-control OR of 1.12 (0.63–1.98). The OR for time trends of ampicillin/amoxicillin was 1.04 (0.77–1.39), resulting in a case–time-control OR of 1.16 (0.55–2.45).

To examine the assumption of no-carryover effect, we used data from NBDPS where history of medication use is collected up to 3 months before conception. When we allowed for a 1-month gap between the case and control period in the COC failure cases from the NBDPS, the OR was 1.45 (0.85–2.50) for overall antibiotics and 1.55 (0.72–3.30) for ampicillin/amoxicillin (Table 2). Adjusting for occurrence of urinary tract infection and upper respiratory tract infection did not materially change the results. In the case–time-control analysis, the OR for time trends of overall antibiotic use was 0.94 (0.76–1.17); after adjusting for this time trend, the case–time-control OR was 1.55 (0.86–2.79). The OR for time trends of ampicillin/amoxicillin use was 0.92 (0.67–1.25); after adjusting for this time trend, the case–time-control OR was 1.69 (0.74–3.83).

Neither acetaminophen nor ibuprofen use was associated with an increased risk of COC failure. In the analysis without a gap between the case and control period, the OR was 0.80 (0.51–1.24) for acetaminophen and 0.52 (0.26–1.05) for ibuprofen; the case–time-control OR was 0.65 (0.41–1.01) for acetaminophen and 0.75 (0.37–1.52) for ibuprofen. When we allowed a 1-month gap between the case and control period among COC failure cases from the NBDPS, the OR was 1.28 (0.76–2.16) for acetaminophen and 0.65 (0.32–1.31) for ibuprofen. After adjusting for time trends, the case–time-control OR was 0.84 (0.50–1.42) for acetaminophen and 0.90 (0.44–1.83) for ibuprofen.

4. Discussion

In this case-crossover study, the OR between antibiotic use and the risk of breakthrough pregnancy during the month following treatment was 1.08 (95% CI: 0.63–1.83) when we used the preceding month as the control window. Allowing a gap of 1 month between the case and control windows in a subgroup of women participating in the NBDPS resulted in an OR of 1.45 (0.85–2.50). None of the analyses reached statistical significance at the .05 level. To our knowledge, this is the largest study to examine this topic.

The purported mechanism of breakthrough pregnancy associated with concomitant antibiotic use primarily involves enterohepatic recirculation of COCs. In the liver, ethinyl estradiol, the estrogen component in most COCs, is metabolized to form inactive conjugates, which are then excreted in the bile [1–4]. However, enzymatic activity of intestinal bacterial flora can break down these conjugates, releasing active ethinyl estradiol for reabsorption. Broad-spectrum antibiotics may disrupt the gut bacterial flora, leading to a decrease in intestinal reabsorption of COCs and a consequent reduction in circulating levels of COCs required to achieve contraception. Other proposed mechanisms include antibiotic-associated interference in absorption, increase in excretion, alterations in plasma-protein binding of COCs and, at least for rifampin, induction of hepatic microsomal enzyme [1–3].

Evidence of the association, or lack thereof, between antibiotics and COC failure has largely come from individual case reports, case series and spontaneous adverse reaction reports; pharmacokinetic studies with very small number of subjects; and small observational studies of primarily long-term antibiotic users. Case series and spontaneous adverse reaction reports suggesting such an association often lack an appropriate control group [13,14]. Pharmacokinetic studies do not appear to support an effect of antibiotics on the plasma levels of COCs (except for rifampin), but a number of studies have suggested that some women might be more susceptible to an antibiotic-induced decrease in plasma concentration of COCs [1–3]. Several clinical studies have found higher risks of pregnancies among COC users with concomitant antibiotic therapy when compared to those without concomitant use [15] or to external controls [16,17], but these higher risks were still within a ‘normal’ range of 1–3% found in typical COC users. In addition, these studies largely included patients from dermatology clinics [15–17], and their findings may not be applicable to other patients.

The ideal design to assess a causal effect of antibiotics on COC failure would be infeasible and unethical, as it would involve randomizing thousands of COC users to antibiotics and studying COC failures without adding further contraceptive protection. Even in a hypothetical large observational cohort study with detailed monitoring of COC and antibiotic use and recording of timing of conception, evaluation of COC failure could be biased by residual confounding due to factors associated with both infections and breakthrough pregnancy, including socioeconomic determinants, sexual behavior, compliance with treatments, and physiologic characteristics. A case-control study could compare antibiotic exposure in COC failure cases with a control group of COC users who did not get pregnant. This design could still be biased because these two distinct groups of women may differ in measured and unmeasured characteristics that could confound the results.

Comparing the pattern of antibiotic use between two periods in the same women may offer several advantages over the more conventional approach. The self-matched design effectively avoids control (subject) selection bias and any confounding factors that remain unchanged during the

few months around conception. A case-crossover study is particularly appropriate for our study because such design has the greatest utility in studies of intermittent exposures with immediate and transient effects on abrupt outcomes [9,18]. In this study, more than 80% of antibiotic treatments were short-term (14 days or less), and studies have shown that antibiotic-associated changes in fecal flora are normally reversed by 10–14 days after stopping of treatment [19,20].

Several limitations need to be addressed, however. First, the assumption of no-carryover effect might be violated because we did not allow for a large enough gap between the case and control period in the primary analysis. To examine the robustness of our results, we created a 1-month "wash-out" gap between the case and control period in the subset of COC failure cases interviewed in the NBDPS and observed a higher OR. Whether this reflected the sensitivity of our findings to the selection of control period warrants further investigation. Second, the assumption of constant frequency of antibiotic use during the 8 weeks before conception among COC users might be violated if there were such a trend. After accounting for potential time trends of antibiotic use, the case–time-control OR suggested a higher risk, although the 95% CI still included one.

Third, although the self-matching adjusts for between-person confounding by design, characteristics that change during the 8 weeks before conception within person and that are associated with antibiotics use (e.g., frequency of sexual intercourse and infections, concomitant medications) might still confound the association between antibiotics and COC failure. The results in the pooled analysis were similar when we adjusted for factors that might vary over time. Nonetheless, it is possible that other events occurring just prior to conception, but which were not considered in our analysis, might have led to a lower use of antibiotics and an underestimation of the effect, as suggested by lower than expected ORs of acetaminophen and ibuprofen. While a close temporal proximity between the case and control period reduced the potential for time trends in antibiotic use and changes in women's characteristics that might confound our findings, it also introduced a high correlation of antibiotic use between two periods — which might partially explain why we observed an effect closer to the null. Fourth, our analyses might have excluded COC failure cases that resulted in pregnancy termination. Such exclusion would affect our results if COC failures associated antibiotic use had a higher or lower probability to be terminated than other COC failures. Fifth, many of the so-called COC failures might be due to missing pills. Restricting the analysis to breakthrough pregnancies among women with perfect compliance (something we could not do in this study) might result in different OR estimates for concomitant antibiotic use.

One of the main strengths of the current study is the access to data on real use of COCs and on date of last menstrual period based mostly on first trimester ultrasound. Electronic health care databases that contain prescriptions or dispensing claims for medications may be less suited to study the effect of antibiotic use on COC failure because the narrow risk window requires accurate information on exposure status around conception. These databases are prone to exposure misclassification because they often lack information needed to determine the date of conception, such as gestational age at birth and last menstrual period [21]. Additionally, electronic prescribing and dispensing information may not accurately reflect whether or when the women took their pills relative to the time of conception. Date of conception and time of COC discontinuation are critical for evaluating failure. On the other hand, information bias due to imperfect recall of medication use around conception is often an issue in interview-based studies. Although women would probably remember if they got pregnant while on the pill, their recall of timing of antibiotic use in relation to the date of conception might be inaccurate, which would tend to dilute the associations under most scenarios. The case-only design is not affected by differential recall among case and control subjects since it compares two time periods within the same subject. However, there could be recall bias due to differential recall of antibiotic use over time around conception. This might lead to over- or underestimation of antibiotic use in the case or control period, and could bias our results in either direction.

In conclusion, we did not find an association between concomitant antibiotic use and the risk of breakthrough pregnancy among COC users. This study cannot rule out an increased risk of COC failure with concurrent antibiotic use due to its limited power, but the data support the pharmacokinetic and pharmacodynamic data of limited effect of antibiotics on contraceptive steroid metabolism.

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